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(54) Title: CYANOACRYLATE COMPOSITIONS COMPRISING A SOLUBLE ANTIMICROBIAL AGENT

(57) Abstract

Disclosed are cyanoacrylate compositions comprising a compatible antimicrobial agent and, in particular, a compatible iodine containing antimicrobial agent. These compositions provide for *in situ* formation of an antimicrobial polymeric cyanoacrylate film on mammalian skin.

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# CYANOACRYLATE COMPOSITIONS COMPRISING A SOLUBLE ANTIMICROBIAL AGENT

## CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation-in-part of U.S. Patent Application Serial No. 09/215,078 filed on December 18, 1998 which application is incorporated herein by reference in its entirety.

## BACKGROUND OF THE INVENTION

### Field of the Invention

This invention is directed to cyanoacrylate prepolymer compositions comprising a soluble and compatible antimicrobial agent and, in particular, an iodine containing antimicrobial agent. These compositions provide for *in situ* formation of antimicrobial polymeric cyanoacrylate films on mammalian skin which films are useful as wound dressings, wound bandages, surgical incise drapes, wound closure materials which replace or are an adjunct to sutures, and the like.

This invention is also directed to kits of parts comprising such prepolymer compositions and an applicator means for applying the composition to mammalian skin.

### References

The following publications, patent applications and patents are cited in this application as superscript numbers:

[1] Hawkins, et al., *Surgical Adhesive Compositions*, U.S. Patent No. 3,591,676, issued July 6, 1971

[2] Halpern, et al., *Adhesive for Living Tissue*, U.S. Patent No. 3,667,472, issued June 6, 1972

[3] McIntire, et al., *Process for the Preparation of Poly(α-Cyanoacrylates)*, U.S. Patent No. 3,654,239, issued April 4, 1972

[4] Barley, et al., *Methods for Treating Non-Suturable Wounds by Use of Cyanoacrylate Adhesives*, International Patent Application Publication No. WO 93/25196, published December 23, 1993

[5] Barley, et al., *Methods for Treating Suturable Wounds by Use of Sutures and Cyanoacrylate Adhesives*, U.S. Patent No. 5,254,132, issued October 19, 1993

[6] Barley, et al., *Methods for Reducing Skin Irritation From Artificial Devices by Use of Cyanoacrylate Adhesives*, U.S. Patent No. 5,653,789, issued August 5, 1997

[7] Rabinowitz, et al., *Method of Surgically Bonding Tissue Together*, U.S. Patent No. 3,527,224, issued September 8, 1970

[8] Kronenthal, et al., *Surgical Adhesives*, U.S. Patent No. 3,995,641, issued December 7, 1976

[9] Davydov, et al., *Medical Adhesive*, U.S. Patent No. 4,035,334, issued July 12, 1977

[10] Waniczek, et al., *Stabilized Cyanoacrylate Adhesives Containing Bis-Trialkylsilyl Esters of Sulfuric Acid*, U.S. Patent No. 4,650,826, issued March 17, 1987

[11] Askill, et al., "*Methods for Draping Surgical Incision Sites*" U.S. Patent No. 5,807,563, issued September 15, 1998

[12] Greff, et al., *Cyanoacrylate Adhesive Compositions,* U.S. Patent No. 5,480,935, issued January 2, 1996

[13] Greff, et al., *Cyanoacrylate Compositions Comprising an Antimicrobial Agent,* U.S. Patent No. 5,684,042, issued on November 4, 1997

[14] Greff, et al., *Cyanoacrylate Compositions Comprising an Antimicrobial Agent,* U.S. Patent No. 5,783,177 issued on July 21, 1998.

[15] Greff, et al., *Cyanoacrylate Compositions Comprising an Antimicrobial Agent,* U.S. Patent No. 5,762,919 issued on June 9, 1998

[16] Greff, et al., *Cyanoacrylate Compositions Comprising an Antimicrobial Agent,* U.S. Patent No. 5,811,091 issued on September 22, 1998.

[17] O'Sullivan, et al., *High Viscosity Cyanoacrylate Adhesive Compositions, and Process for Their Preparation*, U.S. Patent No. 4,038,345, issued July 26, 1977

[18] Beller, et al., *Process for the Preparation of Iodine-Polyvinylpyrrolidone by Dry Mixing*, U.S. Patent No. 2,706,701, issued April 19, 1955

[19] Hosmer, *Process of Stabilizing Polyvinylpyrrolidone*, U.S. Patent No. 2,826,532, issued March 11, 1958

[20] Siggin, *Preparation of Iodine Polyvinylpyrrolidone Adducts*, U.S. Patent No. 2,900,305, issued August 18, 1958

[21] Joyner, et al., *Plasticized Monomeric Adhesive Compositions and Articles Prepared Therefrom*, U.S. Patent Nos. 2,784,127, issued March 5, 1957

[22] Columbus, et al., *Adhesive Cyanoacrylate Compositions with Reduced Adhesion to Skin*, U.S. Patent No. 4,444,933, issued April 24, 1984

[23] Leung, et al., *Biocompatible Monomer and Polymer Compositions*, U.S. Patent No. 5,328,687, issued July 12, 1994

[24] Byram, et al., *Use of Cyanoacrylate Adhesive Compositions to Inhibit Acute Radiation-Induced Skin Damage*, U.S. Patent No. 5,554,365, issued September 10, 1996.

[25] Leplyanin, "*Medical and Surgical Adhesive Composition and Process for Its Preparation*", International Application Publication No. WO 96/23532 published August 8, 1996

[26] Tighe, et al., "*Use of Cyanoacrylate Adhesives for Providing a Protective Barrier Film for the Skin*", U.S. Patent No. 5,580,565, issued on December 3, 1996.

[27] Franklin, et al., *"Process for the Production of a Polymeric Carbamate"*, U.S. Patent No. 4,243,798, issued January 6, 1981.

[28] Erdman, et al., *"Dispersant Lubricating Oil Additives"*, U.S. Patent No. 4,548,722, issued October 22, 1985

[29] Buckley, III, *"Fuel Compositions Containing Very Long Chain Alkylphenyl Poly(oxyalkylene) Aminocarbamates"*, U.S. Patent No. 4881,945, issued November 21, 1989

[30] Bolduc, *"Aerosol Spray System"*, U.S. Patent No. 5,154,320, issued October 13, 1992

[31] Blum, et al., *In vitro Determination of the Antimicrobial Properties of Two Cyanoacrylate Preparations*, J. Dent. Res., 54(3):500-503 (1975)

[32] Berger, et al., *Mixed Cyanoacrylate Ester Compositions,* U.S. Patent No. 5,998,472 issued December 7, 1999

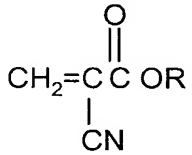
[33] Greff, et al., *"Methods for Sterilizing Cyanoacrylate Compositions",* U.S. Patent Application No. 09/172,858, filed October 15, 1998

All of the above publications, patent applications and patents are herein incorporated by reference in their entirety to the same extent as if each individual publication, patent application or patent was specifically and individually indicated to be incorporated by reference in its entirety.

State of the Art

Cyanoacrylate esters have been disclosed for a variety of topical uses on mammalian skin including use as a replacement or adjunct for sutures or staples in closing the dermal layer of an incision after surgery.[1,2,5] Other disclosed topical uses include use as a hemostat[3], use in covering small non-suturable wounds on skin surfaces[4], use in inhibiting surface skin irritation arising from friction between the skin surface and artificial devices such as tapes, prosthetic devices, casts, etc.[6] and use in inhibiting acute radiation-induced skin damage.[24] Still another topical use of cyanoacrylate esters is its use in the *in situ* formation of a surgical incise drape.[11] In each case, when topically applied to mammalian skin, the cyanoacrylate rapidly polymerizes, typically within a minute, to form a coherent polymeric film which strongly adheres to the skin.

Cyanoacrylate esters suggested for such uses include the following structures:




I

wherein R is an alkyl or other suitable substituent. Such cyanoacrylate esters are disclosed in, for example, U.S. Patent Nos. 3,527,224; 3,591,676; 3,667,472; 3,995,641; 4,035,334; and 4,650,826.[1,2,7-10]

Cyanoacrylate ester compositions for application to mammalian tissue typically are formulated to contain both a plasticizer to enhance flexibility of the resulting polymeric film and a polymerization inhibitor to avoid premature polymerization of the composition. When employed topically on mammalian skin, Greff et al.[12] disclose that the cyanoacrylate composition preferably employs from about 50 to about 500 ppm sulfur dioxide as the polymerization inhibitor and from about 18-25 weight percent of a biocompatible plasticizer such as dioctyl phthalate. Alternatively, Berger, et al.[32] discloses cyanoacrylate ester compositions comprising a $C_{10}$ to $C_{12}$ cyanoacrylate ester which can be used in place of or in conjunction with the biocompatible plasticizer.

Notwithstanding the beneficial properties associated with such cyanoacrylate ester compositions and their suitability for application to mammalian tissue, these compositions do not possess a sufficiently broad spectrum of antimicrobial activity including activity against microbial spores[31] and, accordingly, cannot assure reductions in microbial populations on mammalian tissue either under or adjacent a polymeric cyanoacrylate film formed *in situ* on the tissue.

To address this concern, Greff, et al.[13-16] discloses cyanoacrylate ester compositions comprising a compatible, broad spectrum antimicrobial agent. These compositions are exemplified by the addition of sufficient amounts of polyvinylpyrrolidone/iodine (PVP-$I_2$) into the cyanoacrylate ester composition such that the polymer resulting by *in situ* polymerization of this composition on mammalian skin has antimicrobial properties.

Notwithstanding the significant advancement such PVP-$I_2$ cyanoacrylate compositions represent, PVP-$I_2$ is not soluble in the cyanoacrylate ester and, upon addition, a suspension of PVP-$I_2$ in the cyanoacrylate ester is formed. In order to ensure that a homogeneous composition is applied to mammal skin, it may be necessary to vigorously shake such compositions prior to application. In addition, the presence of insoluble particles dictates against sterilization of these compositions by filtration through small pore biofilters.

In view of the above, a composition comprising a cyanoacrylate ester and a compatible antimicrobial agent soluble therein would be particularly beneficial.

## SUMMARY OF THE INVENTION

This invention is directed to cyanoacrylate ester compositions comprising an antimicrobially effective amount of a complex of iodine molecules with a biocompatible polymer which complex is soluble in the cyanoacrylate ester or esters. These compositions provide for *in situ* formation of an antimicrobial polymeric cyanoacrylate film on mammalian skin and other mammalian tissues such as mucous membranes, etc.

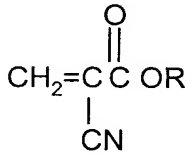
The specific antimicrobial iodine complex employed is soluble in the cyanoacrylate ester or esters and, in addition, is compatible with this ester insofar as the iodine complex neither causes premature polymerization nor prevents polymerization of the monomer, rather a flexible and durable polymeric film is formed *in situ* on mammalian skin and other mammalian tissues by this composition.

Accordingly, in one of its composition aspects, this invention is directed to an antimicrobial cyanoacrylate composition which comprises:

(a) a polymerizable cyanoacrylate ester; and

(b) an antimicrobially effective amount of a complex of iodine molecules with a biocompatible polymer which complex is soluble in said polymerizable cyanoacrylate ester.

Preferably, the polymerizable cyanoacrylate ester (or esters) is/are a polymerizable monomer or reactive oligomer of a cyanoacrylate ester. Such monomers and reactive oligomers are sometimes referred to herein simply as "prepolymers" and, in monomeric form, are preferably represented by formula I:



I

wherein R is selected from the group consisting of:

alkyl of 1 to 20 carbon atoms,

alkenyl of 2 to 20 carbon atoms,

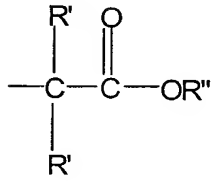
cycloalkyl groups of from 5 to 8 carbon atoms,

phenyl,

2-ethoxyethyl,

3-methoxybutyl,

and a substituent of formula II:



II

wherein each R′ is

independently selected from the group consisting of:

hydrogen and methyl, and

R″ is selected from the group consisting of:

alkyl of from 1 to 6 carbon atoms,

alkenyl of from 2 to 6 carbon atoms,

alkynyl of from 2 to 6 carbon atoms,

cycloalkyl of from 3 to 8 carbon atoms,

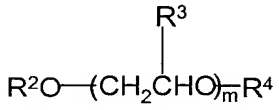
aralkyl selected from the group consisting of benzyl, methylbenzyl and phenylethyl,

phenyl, and

phenyl substituted with 1 to 3 substituents selected from the group consisting of hydroxy, chloro, bromo, nitro, alkyl of 1 to 4 carbon atoms, and alkoxy of from 1 to 4 carbon atoms.

More preferably, in the cyanoacrylate esters of formula I, R is alkyl of from 2 to 20 carbon atoms and still more preferably alkyl of from 4 to 12 carbon atoms. Even more preferably, R is butyl, pentyl, octyl, decyl or dodecyl and most preferably, R is *n*-butyl.

The soluble antimicrobial complexes of iodine molecules with a biocompatible polymer are preferably iodine complexes of polyoxyalkylene polymers. Such polymers are preferably homopolymers and copolymers, including random and block copolymers, which are represented by formula III:



III

wherein $R^2$ is selected from the group consisting of hydrogen and a hydrocarbyl group of from 1 to 30 carbon atoms; each $R^3$ is independently selected from the group consisting of hydrogen and alkyl of 1 to 3 carbon atoms; $R^4$ is selected from the group consisting of hydrogen and a hydrocarbyl group of from 1 to 30 carbon atoms; and *m* is an integer from 1 to 400 and preferably 1 to 300;

with the proviso that the iodine complex of the polymers of formula III have a solubility of at least 5 mg/mL in the cyanoacrylate ester composition at 20°C and preferably at least 10 mg/mL in the cyanoacrylate ester composition.

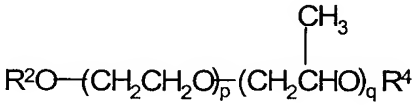
The soluble antimicrobial iodine complexes described herein preferably have an iodine content of from 1 to 30 weight percent based on the weight of the complex; more preferably 5 to 25 weight percent; and most preferably 10 to 20 weight percent.

Preferably, $R^2$ is selected from the group consisting of hydrogen and alkylphenyl and $R^4$ is preferably hydrogen.

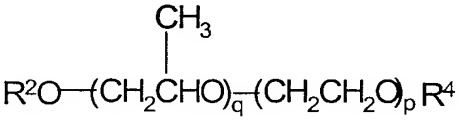
In another preferred embodiment, $R^3$ is hydrogen or methyl.

Even more preferably, the polymers of formula III are polyoxyethylene/polyoxypropylene copolymers ($R^3$ is hydrogen or methyl) which polymers are random copolymers (each $R^3$ is randomly hydrogen or methyl);

block copolymers defined by formula IV and V:



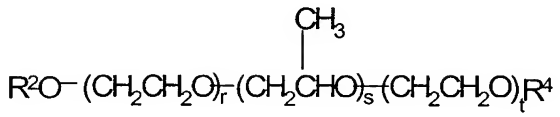
IV



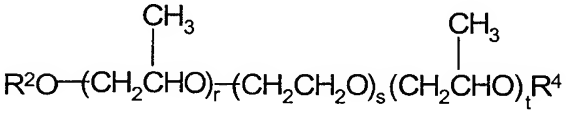
V

where $R^2$ and $R^4$ are as defined above and *p* and *q* are integers independently equal to 1 to 400 and preferably 1 to 200;

or block terpolymers represented by formulas VI and VII:



VI



VII

where $R^2$ and $R^4$ are as defined above and *r*, *s* and *t* are integers independently equal to 1 to 400 and preferably 1 to 100.

It is contemplated that other soluble antimicrobial complexes of iodine molecules with a biocompatible polymer include complexes of iodine with polymethyl methacrylate, polycyanoacrylate, and the like.

The antimicrobial cyanoacrylate compositions described herein preferably further comprise an effective amount of a polymerization inhibitor which is preferably selected from the group consisting of sulfur dioxide, glacial acetic acid, hydroquinone, hindered phenols (e.g., 4-methoxyphenol) and mixtures thereof. In a particularly preferred embodiment, the polymerization inhibitor is a mixture of a biocompatible acid polymerization inhibitor and a biocompatible free radical polymerization inhibitor both of which are employed in combination to inhibit polymerization of the cyanoacrylate ester. The preferred mixture of polymerization inhibitors is a biocompatible acid polymerization inhibitor such as sulfur dioxide, glacial acid acid and other well known acid polymerization inhibitors and a biocompatible free radical polymerization inhibitor including hydroquinone and hindered phenols (e.g., 4-methoxyphenol). The acid polymerization inhibitor is preferably $SO_2$ which is preferably employed at from about 50 to 1000 ppm, more preferably from about 50 to 200 ppm, based on the total weight of the composition. The free radical inhibitor is preferably a mixture of hydroquinone and 4-methoxyphenol. This mixture is employed to stabilize the composition especially during sterilization (e.g., heat, radiation, etc. sterilization methods).

A preferred mixture of these two free radical inhibitors comprises from about 100 to 2000 ppm; more preferably from about 100 to about 1500 ppm; and even more preferably from about 600 to 1200 ppm and is preferably employed at a 10:1 to 1:10 ratio of hydroquinone to 4-methoxyphenol. A particularly preferred mixture of polymerization inhibitors includes 100 ppm sulfur dioxide, 500 ppm

hydroquinone, and 500 ppm 4-methoxyphenol. Another preferred mixture of polymerization inhibitors includes100 ppm sulfur dioxide, 400 ppm hydroquinone, 400 ppm 4-methoxyphenol and 1000 ppm acetic acid.

In yet a further preferred embodiment, the cyanoacrylate compositions described herein further comprise a sufficient amount of a biocompatible plasticizer to enhance the flexibility of the resulting polymeric cyanoacrylate film. Preferred biocompatible plasticizers include, for example, dioctyl phthalate and/or tri-*n*-butyl acetyl citrate and are preferably employed at from about 18 to 25 weight percent based on the total weight of the composition absent the antimicrobial agent. Alternatively, instead of or in addition to incorporating a separate plasticizer into the composition, the cyanoacrylate composition can comprise an effective amount of a $C_{10}$-$C_{12}$ alkyl cyanoacrylate ester as described by Berger, et al.[32]

This invention is also directed to kits useful for applying the antimicrobial cyanoacrylate compositions described herein onto mammalian skin. In particular, such a kit of parts comprises:

(a) a container comprising therein an antimicrobial prepolymeric composition as described above; and

(b) an applicator means for applying the composition onto mammalian skin.

## DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

This invention is directed, in part, to cyanoacrylate compositions comprising an antimicrobially effective amount of a soluble, compatible iodine containing antimicrobial agent. However, prior to discussing this invention in further detail, the following terms will first be defined.

Definitions

As used herein, the following terms have the following meanings:

The term "cyanoacrylate ester compositions" or "cyanoacrylate compositions" refers to polymerizable formulations comprising polymerizable cyanoacrylate ester monomers and/or oligomers which, in their monomeric form, are preferably compounds represented by formula I as described above. Such compositions are sometimes referred to herein as prepolymeric compositions.

More preferably, in formula I, R is an alkyl group of from 2 to 20 carbon atoms including, by way of example, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, *n*-pentyl, *iso*-pentyl, *n*-hexyl, *iso*-hexyl, 2-ethylhexyl, *n*-heptyl, *n*-octyl, nonyl, decyl and dodecyl. More preferably, R is butyl, pentyl, octyl, decyl or dodecyl and most preferably, R is *n*-butyl. Mixtures of such compounds can also be employed.

Polymerizable cyanoacrylate esters are known in the art and are described in, for example, U.S. Patent Nos. 3,527,224; 3,591,676; 3,667,472; 3,995,641; 4,035,334; and 4,650,826[1,2,7-10] the disclosures of each are incorporated herein by reference in their entirety.

A particularly preferred cyanoacrylate ester for use in the invention is *n*-butyl-2-cyanoacrylate and mixtures of *n*-butyl-2-cyanoacrylate with $C_{10}$-$C_{12}$ alkyl cyanoacrylate esters as described by Berger, et al.[32]

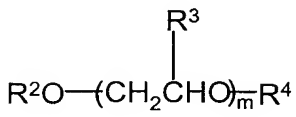
The polymerizable cyanoacrylate ester compositions described herein rapidly polymerize in the presence of water vapor or tissue protein, and the *n*-butyl-cyanoacrylate bonds mammalian tissue without causing histotoxicity or cytotoxicity.

Such polymerizable cyanoacrylate esters are sometimes referred to herein as prepolymers and compositions comprising such esters are sometimes referred to herein as prepolymer compositions.

The term "a complex of iodine molecules with a biocompatible polymer which is soluble in the cyanoacrylate ester" refers to an antimicrobial complex formed by the addition of iodine ($I_2$) to a biocompatible polymer which complex is soluble in the cyanoacrylate ester composition at a concentration of at least 5 mg complex per mL of cyanoacrylate at 20°C and more preferably at least 10 mg/mL. Such complexes are known in the art and are in some cases commercially available. These complexes, on contact with mammalian tissue, are antimicrobial apparently by providing for a source of antimicrobial iodine. In any event, such complexes are employed only as starting materials herein and, by themselves, do not form a part of this invention.

These complexes are sometimes referred to herein simply by the term "soluble iodine/polymer complexes". Such soluble iodine/polymer complexes are distinguished from antibiotics which are naturally derived materials from either bacteria or fungi and whose mode of action is to interfere with bacterial processes resulting in bacterial death. Contrarily, the complexes used in this invention are indiscriminate in destroying any microbes including fungi, viruses and bacteria apparently by release of iodine into the microbes and, accordingly, are properly referred to as antimicrobial agents.

Preferred iodine/polymer complexes for use in the compositions of this invention are iodine complexes of polymers represented by formula III:



III

wherein $R^2$ is selected from the group consisting of hydrogen and a hydrocarbyl group of from 1 to 30 carbon atoms; each $R^3$ is independently selected from the group consisting of hydrogen and alkyl of 1 to 3 carbon atoms; $R^4$ is selected from the group consisting of hydrogen and a hydrocarbyl group of from 1 to 30 carbon atoms; and *m* is an integer from 1 to about 400 and preferably 1 to 300;

with the proviso that the iodine complex of the polymers of formula III have a solubility of at least 5 mg/mL in the cyanoacrylate ester composition at 20°C and preferably at least 10 mg/mL.

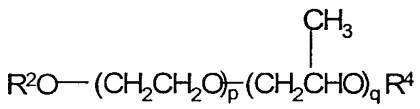
It is understood that the integer *m* represents a number average of oxyalkylene groups wherein individual members have more or less than the average number.

The soluble antimicrobial iodine complexes described herein preferably have an iodine content of from 1 to 30 weight percent based on the weight of the complex; more preferably 15 to 25 weight percent; and most preferably 20 weight percent.

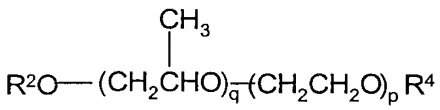
Preferably, $R^2$ is selected from the group consisting of hydrogen and alkylphenyl and $R^4$ is preferably hydrogen. In another preferred embodiment, $R^3$ is hydrogen or methyl.

Even more preferably, the polymers of formula III are polyoxyethylene/polyoxypropylene copolymers ($R^3$ is hydrogen or methyl) which polymers are random copolymers (each $R^3$ is randomly hydrogen or methyl);

block copolymers defined by formula IV and V:



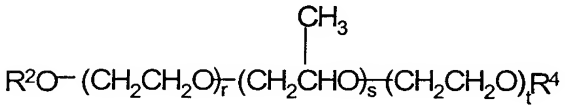
IV



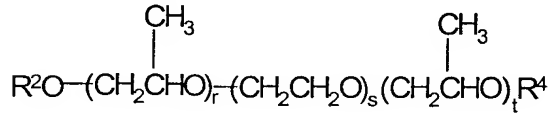
V

where $R^2$ and $R^4$ are as defined above and $p$ and $q$ are integers independently equal to 1 to 400 and preferably 1 to 200;

or block terpolymers represented by formulas VI and VII:



VI



VII

where $R^2$ and $R^4$ are as defined above and $r$, $s$ and $t$ are integers independently equal to 1 to 400 and preferably 1 to 100.

Such iodine/polymers complexes are commercially available from, for example, WestAgro, Kansas City, Missouri, USA. Alternatively, methods for preparing iodine complexes by iodinating a biocompatible polymer are well known in the art and are described in, for example, U.S. Patent Nos. 2,706,701, 2,826,532 and 2,900,305.[18-20] In addition, the underlying polymers are well known materials available, for example, from Aldrich Chemical Company, Milwaukee, Wisconsin, USA as either a di-alcohol polymer ($R^2$ and $R^4$ are hydrogen), a monocapped, mono-alcohol polymer ($R^2$ is hydrocarbyl and $R^4$ is hydrogen) and a dicapped polymer ($R^2$ and $R^4$ are hydrocarbyl). In addition, monocapped products are described in numerous patents including, by way of example only, U.S. Patent Nos. 4,243,798; 4,548,722; and 4,881,945[27-29] each of which is incorporated herein by reference in its entirety.

Particularly preferred soluble iodine/polymer complexes include iodine complexes with alpha-(p-nonylphenyl)-omega-hydroxypoly(oxyethylene) [i.e., in Formula III, $R^2$ = nonylphenyl; $R^3$ = hydrogen; and $R^4$ = H]; iodine complexes with polyethyoxy polypropoxy polyethoxy ethanol. Both of these complexes can

be produced in the laboratory or purchased from commercial sources. Alternatively, a soluble biocompatible polymer can be added to the cyanoacrylate ester along with iodine to form the iodine/polymer complex *in situ*.

The term "biocompatible plasticizer" refers to any material which is soluble or dispersible in the cyanoacrylate composition, which increases the flexibility of the resulting polymer film coating on the skin surface, and which, in the amounts employed, is compatible with the skin as measured by the lack of moderate to severe skin irritation. Suitable plasticizers are well known in the art and include those disclosed in U.S. Patent Nos. 2,784,127[21] and 4,444,933[22] the disclosures of both of which are incorporated herein by reference in their entirety. Specific plasticizers include, by way of example only, tri-*n*-butyl acetyl citrate (preferably ~20 weight percent or less), acetyl trihexyl citrate (preferably ~20 weight percent or less) butyl benzyl phthalate, dibutyl phthalate, dioctylphthalate, *n*-butyryl tri-*n*-hexyl citrate, diethylene glycol dibenzoate (preferably ~20 weight percent or less). The particular biocompatible plasticizer employed is not critical and preferred plasticizers include tri-*n*-butyl acetyl citrate.

The term "polymerization inhibitor" refers to conventional inhibitors of cyanoacrylate esters including materials such as sulfur dioxide, glacial acetic acid, hydroquinones, 4-methoxyphenol, combinations of such materials, and the like. The polymerization inhibitor is typically employed in amounts effective to inhibit polymerization until application onto the mammalian skin.

The term "hydrocarbyl" refers to an organic radical or group composed of carbon and hydrogen which may be aliphatic, alicyclic, aromatic or combinations thereof, e.g., aralkyl. Preferably, the hydrocarbyl group will be relatively free of aliphatic unsaturation, i.e., ethylenic and acetylenic, particularly acetylenic unsaturation. The hydrocarbyl group preferably contains from 1 to 30 carbon atoms and more preferably from 1 to 20. When the hydrocarbyl group is aralkyl, the aralkyl group preferably contains from 7 to 30 carbon atoms.

The term "antimicrobial agent" refers to agents which destroy microbes (i.e., bacteria, fungi, viruses and microbial spores) thereby preventing their development and pathogenic action.

Compositions

This invention is based on the novel and unexpected discovery that the iodine/polymer complexes described herein are both compatible with and soluble in cyanoacrylate esters forming a soluble prepolymer composition which, upon polymerization, provides for an antimicrobial cyanoacrylate polymeric film. Compatibility is assessed by the fact that these complexes are dispersible in the cyanoacrylate ester composition at antimicrobially effective concentrations and when so employed, do not cause premature polymerization of the cyanoacrylate ester composition and do not prevent effective polymerization of the cyanoacrylate ester composition when applied to mammalian tissue. Moreover, the polymerizable cyanoacrylate ester composition comprising such complexes forms a flexible, durable polymeric film having the complex incorporated therein which complex is released from the film in sufficient amounts to provide antimicrobial properties to the film.

Solubility is assessed by the fact that these iodine complexes are soluble in the cyanoacrylate ester at a concentration of at least 5 mg/mL at 20°C; preferably at least 10 mg/mL at 20°C; and more at least 30 mg/mL at 20°C. In a particularly preferred embodiment, the concentration of the iodine complex in the composition is from 0.5 to 40 weight percent, more preferably from 1 to 10 weight percent and most preferably from 1 to 5 weight percent.

As shown in the examples below, the soluble compositions of this invention have antimicrobial properties, have prolonged self-life and may be sterile filtered using a 0.2 μm Nylon or Teflon filter.

In one embodiment, the compositions of this invention are prepared by adding the iodine/polymer complex (i.e., the iodophor) to the cyanoacrylate ester composition. Upon addition of the iodine/polymer complex to the cyanoacrylate prepolymer composition, the resulting system is thoroughly mixed to obtain a homogeneous solution. Alternatively, the iodine/polymer complex can be made by direct addition of iodine to a solution of cyanoacrylate ester and polymer. In this method, the polymer of choice is homogeneously mixed with the cyanoacrylate ester, then iodine is added directly to this solution. The resulting system is mixed to obtain a homogeneous solution. Conversely this can be done by first adding iodine to cyanoacrylate ester, then adding a selected polymer to this system.

Care should be taken when selecting commercial iodophors for use in this invention. Specifically, the commercial preparation of these iodophors can affect the performance of the antimicrobial cyanoacrylate composition when applied to the mammalian tissue. For instance, some commercial iodophors have been found to contain large amounts of hydroiodic acid and water. The acid can cause skin irritation and delayed setting. The water and other impurities can cause reduced product life and increased instability. Accordingly, in one embodiment, the iodine/polymer complexes used in the compositions of this invention comprise less than about 10 weight percent water; preferably less than about 1 percent water and more preferably less than about 0.05 weight percent. In another embodiment, the iodine/polymer complexes used in the compositions of this invention comprise less than about 1 weight percent hydroiodic acid; preferably less than about 0.1 percent water and more preferably less than about 0.05 weight percent.

If suitable commercial iodophors cannot be found, iodine/polymer complexes can be readily made by bringing the selected polymer, either in a liquid or powder form, into intimate contact with elemental diatomic iodine with or without heat. Once complexation has occurred, the iodine/polymer complex can be directly added to the cyanoacrylate ester composition.

The amount of iodine/polymer complex added to the cyanoacrylate composition is a sufficient amount such that the resulting polymeric film is antimicrobial. Preferably, from about 0.5 to about 40 weight percent of the iodine/polymer complex and more preferably from about 1 to 10 weight percent is added to the cyanoacrylate composition based on the total weight of the composition.

The specific amount of iodine/polymer complex required to effect antimicrobial properties in the resulting polymeric film can be readily measured by conventional *in vitro* assays measuring zones of microbial growth inhibition around the film. Zones of inhibition of at least 1 millimeter and preferably 3 millimeters from the edge of the film when tested in the manner of Example 10 below evidence that the polymeric film is antimicrobial. Assessing the amount of iodine/polymer complex required in the polymeric film to effect such a zone of inhibition is well within the skill of the art.

The composition of the antimicrobial complex and the cyanoacrylate ester can be formulated to a specific viscosity to meet disparate demands for the intended application of the composition. For example, relatively low viscosities are often preferred where application is to be made to a large surface area (e.g., abdominal surfaces). This preference results from the fact that these forms are less viscous and, accordingly, will permit more facile large surface area application of a thin film. Contrarily, where application is to be made to a more complex curvature of the skin (e.g., elbow surfaces, knee surfaces and the like), higher viscosity compositions, including those containing thixotropic materials, are preferred to prevent "running" of the compositions to unintended locations.

Accordingly, these compositions have a viscosity of from about 2 to 50,000 centipoise at 20°C. For low viscosity applications, viscosity ranges of from about 2 to 500 centipoise at 20°C are preferred. More preferably, the cyanoacrylate ester employed in the composition is almost entirely in monomeric form and the

composition has a viscosity of from about 2 to about 100 centipoise at 20°C. Even more preferably, the cyanoacrylate ester employed in the composition is almost entirely in monomeric form and the composition has a viscosity of from about 5 to about 100 centipoise at 20°C.

A thickening agent is optionally employed to increase the viscosity of the composition which thickening agent is any biocompatible material which increases the viscosity of the composition. Suitable thickening agents include, by way of example, polymethyl methacrylate (PMMA) or other preformed polymers soluble or dispersible in the composition, a suspending agent such as fumed silica and the like, with PMMA being preferred. Fumed silica is particularly useful in producing a gel for topical application having a viscosity of from about 1500 to 50,000. Suitable thickening agents for the cyanoacrylate compositions described herein also include a polymer of the alkyl cyanoacrylate as disclosed in U.S. Patent Nos. 3,654,239[3] and 4,038,345[17] both of which are incorporated herein by reference in their entirety.

Thickening agents are deemed to be biocompatible if they are soluble or dispersible in the composition and are compatible with the skin as measured by the lack of moderate to severe skin irritation.

The cyanoacrylate composition can optionally include a biocompatible plasticizer and, when so employed, such plasticizers are preferably included from about 10 to 30 weight percent and more preferably from about 18 to 25 weight percent based on the weight of the composition absent the antimicrobial agent. Particularly preferred biocompatible plasticizers for use in the compositions described herein are dioctylphthalate, octyl tributyl citrate or tributyl acetyl citrate.

Additionally, the cyanoacrylate compositions described herein preferably include polymerization inhibitors in effective amounts to inhibit premature polymerization of the composition.

The cyanoacrylate ester compositions may additionally contain one or more optional additives such as perfumes, rubber modifiers, modifying agents, etc. In practice, each of these optional additives should be both miscible and compatible with the cyanoacrylate composition and the resulting polymer. Compatible additives are those that do not prevent the use of the cyanoacrylates in the manner described herein.

Perfumes are added to provide a pleasant smell to the formulation. Rubber modifiers are added to further enhance the flexibility of the resulting polymer layer. The amount of each of these optional additives employed in the composition is an amount necessary to achieve the desired effect.

Additionally, the cyanoacrylate composition can optionally comprise a formaldehyde scavenger compound such as those described by Leung, et al.[23] The use of such scavengers has been suggested as enhancing internal *in vivo* applications of cyanoacrylates.

Still further, it is contemplated that the cyanoacrylate composition can optionally comprise an acrylic monomer that will act as a polymeric plasticizer when it copolymerizes with the cyanoacrylate composition. In this regard, a particularly preferred embodiment comprises the addition of a $C_{10}$ to $C_{12}$ cyanoacrylate, an example of which is disclosed by Berger[32]. Other acrylic monomers which can be optionally employed include those disclosed by Leplyanin.[25]

After the composition has been prepared, this composition can optionally be sterilized by, for example, E-beam sterilization techniques in the manner described by Greff, et al.[33] or by sterile filtration through a Nylon or Teflon biofilter having a pore size of no more than 0.22$\mu$m or by $\gamma$-irradiation as disclosed in U.S. Patent No. 5,530,037 which is incorporated herein by reference in its entirety.

Utility

The compositions described herein are useful in forming *in situ* a broad spectrum antimicrobial polymeric film on the tissue surface of a mammalian patient. Such mammalian patients preferably include humans as well as, for example, domestic animals such as horses, cows, dogs, sheep, cats, etc.

The polymeric film finds particular utility in inhibiting microbial contamination thereunder and in the areas immediately adjacent thereto. Accordingly, such polymeric films can be used to topically cover small non-suturable wounds on skin surfaces which wounds do not penetrate through the dermal layer of the skin as in the manner described in Barley, et al.[4] When so employed, the antimicrobial cyanoacrylate composition is applied over the small non-suturable wound. Upon polymerization, an antimicrobial polymeric film is formed over the wound which provides for broad spectrum antimicrobial properties at the wound surface while also preventing exogenous contaminants from entering the wound.

It is further contemplated that the compositions of this invention can be used for the topical treatment of infectious skin diseases by topically applying an antimicrobial effective amount of the compositions of this invention for a sufficient amount of time to ameliorate the condition.

Additionally, the polymeric films formed from the antimicrobial cyanoacrylate compositions described herein can also be used in the *in situ* formation of a surgical incise drape in the manner described by Askill, et al.[11] When so employed, the *in situ* formed film strongly adheres to the mammalian skin surface to provide for a surgical incise drape which does not lift during surgery and has broad spectrum antimicrobial properties.

When used as either a small wound covering or as a surgical incise drape, the antimicrobial polymeric film will only adhere to the skin for a period of about

1-4 days after which time it sloughs off. This occurs because the cyanoacrylate polymer adheres only to the uppermost portion of the epidermal layer which is continuously in the process of being sloughed off and replaced by the underlying cells. Accordingly, the antimicrobial cyanoacrylate film need not be removed after *in situ* formation. However, if removal of the polymeric film is required, such can be accomplished with a material such as acetone (nail polish remover).

Other utilities for the compositions of this invention include their use to form polymeric hemostatic films[3], use to form polymeric films in inhibiting surface skin irritation arising from friction between the skin surface and artificial devices such as tapes, prosthetic devices, casts, etc.[6], use in forming polymeric films in inhibiting acute radiation-induced skin damage[24], use in treating incontinence and areas adjacent to stomas[26] and use as substitutes for sutures, staples, steristrips, and other tissue adhesives in closing surgical wounds.

Kits

In view of the many different uses for application to mammalian tissue, this invention also encompasses a kit of parts useful for applying the antimicrobial cyanoacrylate compositions described herein onto mammalian tissue. In particular, such a kit of parts comprises (a) a container comprising therein an antimicrobial prepolymeric composition as described above and (b) an applicator means for applying the composition to mammalian tissue.

The container comprises any compatible material which stores the cyanoacrylate composition without degradation of the container or prematurely polymerizing the cyanoacrylate prepolymer. Such materials include, by way of example, inorganic materials such as Type 1 glass (including amber glass), ceramics, metals (e.g., aluminum, tin and tin coated tubes), etc. and organic materials such as inert polymers including polyolefins (e.g., high density polyethylene), fluorinated polyolefins, and the like. Examples of suitable

containers include those recited in Bolduc, U.S. Patent No. 5,154,320,[30] which is incorporated herein by reference in it entirety.

Suitable applicator means include brushes, rollers, aerosols, swabs, foams (e.g., polyethylene foam) and the like. A particularly preferred applicator is described in U.S. Patent No. 4,183,684.

In one embodiment, the container and applicator means are combined into a single article such as a brush affixed to the terminal portion of the container wherein means are employed to prevent premature release of the cyanoacrylate prepolymeric composition. For example, the brush may be overlayed with a removable impermeable barrier. When application of the cyanoacrylate prepolymer composition is intended, the barrier is simply removed.

In another embodiment, the container and applicator means are separate articles designed to mate with each other. For example, the cyanoacrylate prepolymer composition could be stored in an amber vial sealed with a screw cap and the applicator means includes a screw mechanism which mates with the screw mechanism on the top of the vial. When application of the cyanoacrylate prepolymer composition is intended, the cap is removed from the vial and the applicator is attached. The particular container/applicator means are not critical and other such means are well within the scope of the skilled artisan including those set forth by Bolduc, U.S. Patent No. 5,154,320.[30]

The following examples illustrate certain embodiments of the invention but are not meant to limit the scope of the claims in any way.

## EXAMPLES

In the examples below, all temperatures are in degrees celsius (unless otherwise indicated) and all percents are weight percent (also unless otherwise

indicated). Additionally, the following abbreviations have the following meanings. If an abbreviation is not defined, it has its generally accepted meaning.

| | | |
|---|---|---|
| g | = | gram |
| kGry | = | kiloGray |
| mL | = | milliliters |
| mm | = | millimeters |
| *n*-bca | = | *n*-butyl cyanoacrylate |
| *n*-dca | = | *n*-decyl cyanoacrylate |
| Pluronics L62 | = | a liquid, blocked copolymer of propylene oxide and ethylene oxide with an average molecular of 2450 and comprising approximately 20 percent ethylene units |
| Pluronics F-68 | = | a solid, blocked copolymer of propylene oxide and ethylene oxide with an average molecular of 8350 and comprising approximately 80 percent ethylene units |
| ppm | = | parts per million |
| TSA | = | trypticase soy agar |

## EXAMPLES 1-6

The following examples illustrate the preparation of several soluble antimicrobial cyanoacrylate compositions. In each of these examples, the cyanoacrylate composition comprises a mixture of the following components:

| | |
|---|---|
| Mixture A: | 80 weight percent of *n*-bca<br>20 weight percent of *n*-dca |
| Mixture B: | 50 weight percent of *n*-bca<br>50 weight percent of *n*-dca |

wherein the recited weight percents are weight percents based solely on the amount of each of the two components. In addition, each of Mixtures A and B comprise the following combination of polymerization inhibitors: 100 ppm $SO_2$, 500 ppm hydroquinone, and 500 ppm 4-methoxyphenol.

Each of the above mixtures were then used to prepare antimicrobial cyanoacrylate compositions by the addition of 0.5 weight percent, 1.5 weight

percent or 3 weight percent, based on the total weight of the composition, of Tamed Iodine III®, an iodine complex of polyethoxy-polypropoxy ethanol (containing approximately 20 weight percent of iodine in the complex) available from WestAgro, Kansas City, Missouri, USA) to provide for Examples 1-6 as illustrated in Table I below:

TABLE I

| Example No. | Mixture | Weight % Tamed III Iodine |
|---|---|---|
| 1 | A | 0.5 |
| 2 | A | 1.5 |
| 3 | A | 3 |
| 4 | B | 0.5 |
| 5 | B | 1.5 |
| 6 | B | 3 |

Each of the compositions was mixed until homogenous and approximately 10 mL of each of these compositions were separately packaged into ampules having a volume of approximately 20 mL. After filling the ampule, the open end of the ampule was capped either with a Teflon lined screw cap or crimp top. To achieve sterilization, the vials were exposed to 20 to 25 kGry of E-beams.

Certain of these compositions were tested for their ability to form a polymeric film on mammalian skin. In all cases, the tested composition cured rapidly upon contact with mammalian skin to provide a flexible and durable film where flexibility was assessed by visual evaluation to determine the ability of the film to be retained on the skin without cracking or peeling for at least 24 hours and durability was assessed by determining whether the film was retained on the skin surface for at least 24 hours

**EXAMPLES 7 to 9**

The following examples were conducted to determine the stability of the cyanoacrylate compositions of this invention under accelerated storage conditions. In each of these examples, the cyanoacrylate composition is *n*-bca to which has been added the following combination of polymerization inhibitors: 100 ppm $SO_2$, 250 ppm hydroquinone, and 250 ppm 4-methoxyphenol.

This mixture was then used to prepare soluble antimicrobial cyanoacrylate compositions by the addition of Tamed Iodine III® which is an iodine complex of polyethoxy polypropoxy ethanol available from WestAgro, Kansas City, Missouri, USA as shown in Table II. The weight concentration of the iodine complex is based on the total weight of the composition.

TABLE II

| Example | Weight % of Tamed Iodine III | Time at 50°C | Equivalent Real Aging |
|---|---|---|---|
| 7 | 10 | 8 weeks | 15 months |
| 8 | 2.5 | 11 weeks | 22 months |
| 9 | 0.6 | 11 weeks | 22 months |

Each of the above formulations (about 10 mL) were added to 20 mL screw capped or crimp capped vials and then stored in a 50°C oven maintained at ambient humidity for the length of time indicated in Table II. Storage under these accelerated aging conditions corresponds to about the number of months stability at ambient storage conditions as indicated in Table II.

At the end of this period, the compositions were removed and evaluated for premature polymerization, presence of solids and ability to form a polymeric film on mammalian skin. In all cases, the compositions did not polymerize under these accelerated storage conditions. In addition, there was no precipitate present in the tested formulations evidencing that the iodine complex did not precipitate from

solution. Finally, as to each composition tested, it rapidly formed a cyanoacrylate film on mammalian skin.

## EXAMPLE 10

The following example was conducted to determine whether the polymeric cyanoacrylate film formed from the compositions of this invention was antimicrobial. Specifically, this example employed the composition of Example 5 (mixture B with 1.5 weight percent of Tamed Iodine III -- , an iodine complex of polyethoxy-polypropoxy ethanol containing approximately 20 weight percent of iodine in the complex available from WestAgro, Kansas City, Missouri, USA) and is referred to herein as the "Test Composition". This composition was tested as follows.

In all cases, a stock solution of the microbe under study was diluted in 0.9% USP sodium chloride for injection to a No. 2 McFarland Standard [provides for $10^6$ to $10^7$ colony forming units (CFU) per mL]. The standardized culture was added to molten Trypticase Soy Agar (TSA) at a 1:100 ratio. The seeded agar was poured into a sterile 100 mm diameter Petri dish and allowed to harden at room temperature. The Test Composition and the control (Penicllin G 1.0 U/mL) were applied directly into penicylinder of the seeded agar. The seeded TSA plate was then incubated at 30-35°C for 24 hours. Following incubation, zones of inhibition were measured in mm. The zone of inhibition was measured for four replicate tests and the average given in Table III below:

Table III

| Microbe | ATCC No. | Zone of Inhibition Test Composition | Zone of Inhibition Control |
|---|---|---|---|
| *Staphylococcus aureus* methicillin resistant | 33591 | 27.2 mm | 8.7 mm |
| *Staphylococcus aureus* | 25923 | 21.7 mm | 10.7 mm |
| *Staphylococcus epidermidis* | 12228 | 7.7 mm | 7.4 mm |
| *Staphylococcus epidermidis* methicillin resistant | 51625 | 11.3 mm | 9.4 mm |
| *Staphylococcus pneumoniae* | 33400 | 10.8 mm | 28.8 mm |
| *Enterococcus faecalis* | 19433 | 7.8 mm | 30.1 mm |
| *Pseudomonas aeruginosa* | 43088 | 7.3 mm | 7.6 mm |
| *Escherichia coli* | 8739 | 7.6 mm | 9.0 mm |
| *Enterococcus faecalis* vancomycin resistant | 51299 | 9.7 mm | 29.0 mm |
| *Klebsiella pneumoniae* | 13883 | 7.4 mm | 7.6 mm |
| *Enterobacter cloacae* | 13047 | 8.6 mm | 8.9 mm |
| *Candida albicans* | 10231 | 6.8 mm | 9.5 mm |
| *Streptococcus pyogenes* | 19615 | 5.3 mm | 31.1 mm |
| *Proteus vulgaris* | 13315 | 32.0 mm | 11.0 mm |
| *Bacillus subtillis* | 6633 | 36.8 mm | 25.7 mm |
| *Serratia marcescens* | 13880 | 10.4 mm | 10.6 mm |

The above data demonstrates that the composition of this invention possesses antimicrobial activity.

## EXAMPLE 11

The following example was conducted to determine whether it was possible to pass the composition composition of Mixture A described in Example 3 through a sterilizing filter assembly.

The monomeric cyanoacrylate composition of Example 3 was passed through a 0.2 μm sterile nylon filter (Millipore Corp, MA) using sterile technique into a sterile vial. The composition passed freely through the filter.

Accordingly, this demonstrates that the compositions of this invention may be readily sterilized by filtration.

## EXAMPLE 12

In this example, several compositions were prepared to demonstrate the ability to form an iodine/polymer complex in situ in the cyanoacrylate ester composition by direct addition of iodine to a solution of cyanoacrylate ester and polymer. In each of these examples, the cyanoacrylate ester and polymer mixture comprised the following components:

| | |
|---|---|
| Mixture C: | 97 weight percent n-butylcyanoacrylate;<br>3 weight percent Pluronics L62; |
| Mixture D: | 77.7 weight percent n-butylcyanoacrylate;<br>19.3 weight percent tributyl-o-acetylcitrate<br>3.0 weight percent Pluronics L62; |

In addition, both Mixtures C and D further contained the following amounts of polymerization inhibitors:

100 ppm $SO_2$
400 ppm hydroquinone
400 ppm 4-methoxyphenol
1000 ppm acetic acid

Each of Mixtures C and D were then used to prepare antimicrobial cyanoacrylate compositions by the addition of 0.3 weight percent of iodine, based on the total weight of the composition. After addition, the compositions were mixed until the iodine dissolved and a homogeneous solution was obtained.

Both compositions were tested for their ability to form a polymeric film on mammalian skin. In both cases, the tested compositions cured rapidly upon contact with mammalian skin to provide a flexible and durable film. The films remained on the skin for at least 24 hours.

**EXAMPLE 13**

This example was conducted to demonstrate the synthesis of an iodine/polymer complex which can be added to the cyanoacrylate ester composition to provide for a homogeneous composition.

Diatomic iodine chips (18 g, Aldrich Chemical Company, Milwaukee, Wisconsin, USA) were added to a polyoxyalkylene polymer (82 g, Pluonics F-68, BASF Corporation, North Mount Olive, New Jersey, USA). The mixture was heated at 60°C with stirring for one hour whereupon the solution was a rich dark brown color.

The resulting iodine/polymer mixture (3 g) was added to n-butyl cyanoacrylate (97 g) formulated with 500 ppm hydroquinone, 500 ppm 4-methoxyphenol and 250 ppm acetic acid. The solution was mixed until homogeneous. A sample of the resulting solution was applied to mammalian skin where it cured rapidly upon contact to form a flexible and durable film (for at least 24 hours).

**EXAMPLE 14**

This example was conducted to demonstrate the synthesis of an iodine/polymer complex in situ by addition of iodine to the cyanoacrylate ester

composition followed by addition of a biocompatible polymer which forms a complex with the iodine.

Diatomic iodine chips (0.3 g) were added to n-butyl cyanoacrylate (9.7 g) and the resulting mixture was slowly agitated until all of the iodine was dissolved. Afterwards, a polyoxyalkylene polymer (3 g, Pluonics L62, BASF Corporation, North Mount Olive, New Jersey, USA) was added to the solution and mixed for five minutes at low agitation until a homogeneous solution was obtained. A sample of the resulting solution was applied to mammalian skin where it cured rapidly.

**EXAMPLE 15**

This example was conducted to demonstrate the affinity of the iodine for the biocompatible polymer rather than the cyanoacrylate ester.

Polyoxyalkylene polymer (3 g, Pluronics L62, BASF Corporation, North Mount Olive, New Jersey, USA) was added to a test tube. Subsequently, n-butyl cyanoacrylate (7 g) was carefully added so as to form a cyanoacrylate ester layer separate from the liquid polymer layer. At this time, diatomic iodine chips (0.1 g) were added to the test tube and dissolved without agitation. During dissolution, the polyoxyalkylene polymer layer became dark brown whereas the cyanoacrylate ester layer remained clear. After one hour, the iodine had totally dissolved and could only be seen in the polyoxyalkylene polymer layer (determined visually). The two layers were then mixed with agitation to form a homogenous solution which, when applied to mammalian skin, rapidly cured to form a polymeric film thereon.

From the foregoing description, various modifications and changes in the composition and method will occur to those skilled in the art. All such modifications coming within the scope of the appended claims are intended to be included therein.

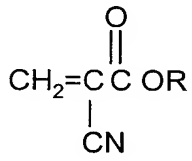
**WHAT IS CLAIMED IS:**

1. An antimicrobial cyanoacrylate composition which comprises:

(a) a polymerizable cyanoacrylate ester; and

(b) an antimicrobially effective amount of a complex of iodine molecules with a biocompatible polymer which complex is soluble in said polymerizable cyanoacrylate ester.

2. The antimicrobial cyanoacrylate composition according to Claim 1 wherein the polymerizable cyanoacrylate ester is a polymerizable monomer or oligomer of a cyanoacrylate ester which, in monomeric form, is represented by formula I or mixtures thereof:



I

wherein R is selected from the group consisting of:

alkyl of 1 to 20 carbon atoms,

alkenyl of 2 to 20 carbon atoms,

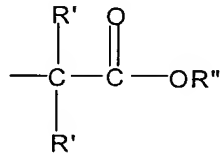
cycloalkyl groups of from 5 to 8 carbon atoms,

phenyl,

2-ethoxyethyl,

3-methoxybutyl,

and a substituent of formula II:



II

wherein each R′ is independently selected from the group consisting of:

hydrogen and methyl, and

R″ is selected from the group consisting of:

alkyl of from 1 to 6 carbon atoms,

alkenyl of from 2 to 6 carbon atoms,

alkynyl of from 2 to 6 carbon atoms,

cycloalkyl of from 3 to 8 carbon atoms,

aralkyl selected from the group consisting of benzyl, methylbenzyl and phenylethyl,

phenyl, and

phenyl substituted with 1 to 3 substituents selected from the group consisting of hydroxy, chloro, bromo, nitro, alkyl of 1 to 4 carbon atoms, and alkoxy of from 1 to 4 carbon atoms.

3. The antimicrobial cyanoacrylate composition according to Claim 2 wherein R is alkyl of from 2 to 20 carbon atoms.

4. The antimicrobial cyanoacrylate composition according to Claim 3 wherein R is alkyl of from 4 to 12 carbon atoms.

5. The antimicrobial cyanoacrylate composition according to Claim 2 wherein R is selected from the group consisting of methyl, butyl, pentyl, octyl, decyl or dodecyl.

6. The antimicrobial cyanoacrylate composition according to Claim 5 wherein R is *n*-butyl.

7. The antimicrobial cyanoacrylate composition according to Claim 1 which further comprises a biocompatible plasticizer.

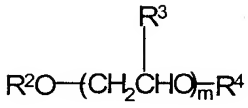
8. The antimicrobial cyanoacrylate composition according to Claim 7 wherein said biocompatible plasticizer is selected from the group consisting of dioctylphthalate, octyl tributyl citrate or tributyl acetyl citrate.

9. The antimicrobial cyanoacrylate composition according to Claim 1 which further comprises a polymerization inhibitor.

10. The antimicrobial cyanoacrylate composition according to Claim 9 wherein said polymerization inhibitor is a mixture comprising hydroquinone and $SO_2$.

11. The antimicrobial cyanoacrylate composition according to Claim 1 wherein said complex of iodine molecules with a biocompatible polymer are iodine complexes of polyoxyalkylene polymers.

12. The antimicrobial cyanoacrylate composition according to Claim 1 wherein the polyoxyalkylene polymers of said iodine complexes of polyoxyalkylene polymers are represented by formula III:



III

wherein $R^2$ is selected from the group consisting of hydrogen and a hydrocarbyl group of from 1 to 30 carbon atoms; each $R^3$ is selected from the group consisting of hydrogen and alkyl of 1 to 3 carbon atoms; $R^4$ is selected from the group consisting of hydrogen and a hydrocarbyl group of from 1 to 30 carbon atoms; and *m* is an integer from 1 to 400;

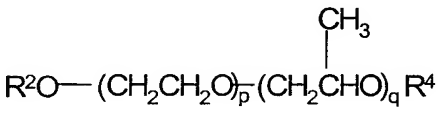
with the proviso that the iodine complex of the polymers of formula III have a solubility of at least 10 mg/ml in the cyanoacrylate ester composition at 20°C.

13. The antimicrobial cyanoacrylate composition according to Claim 12 wherein $R^2$ is selected from the group consisting of hydrogen and alkylphenyl and $R^4$ is hydrogen.

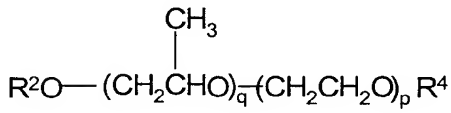
14. The antimicrobial cyanoacrylate composition according to Claim 12 wherein $R^3$ is hydrogen or methyl.

15. The antimicrobial cyanoacrylate composition according to Claim 12 wherein the polymers of formula III are random copolymers comprising oxyethylene and oxypropylene units.

16. The antimicrobial cyanoacrylate composition according to Claim 12 wherein the polymers of formula III are block copolymers defined by formula IV and V:



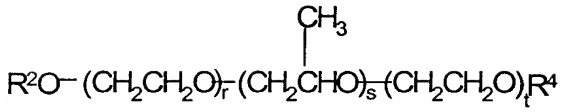
IV



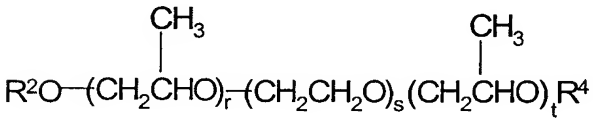
V

where $R^2$ and $R^4$ are as defined above and $p$ and $q$ are integers independently equal to 1 to 400.

17. The antimicrobial cyanoacrylate composition according to Claim 12 wherein the polymers of formula III are block terpolymers represented by formulas VI and VII:



VI



VII

where $R^2$ and $R^4$ are as defined above and *r*, *s* and *t* are integers independently equal to 1 to 400.

18. A method for the preparation of antimicrobial cyanoacrylate compositions which comprises a polymerizable cyanoacrylate ester and an antimicrobially effective amount of a complex of iodine molecules with a biocompatible polymer which complex is soluble in said polymerizable cyanoacrylate ester

which method comprises:

(a) adding a biocompatible polymer to a polymerizable cyanoacrylate ester;

(b) adding diatomic iodine to the composition provided in (a) above and mixing the resulting composition under conditions wherein the iodine complexes with the biocompatible polymer and forms a homogeneous solution

wherein the amount of biocompatible polymer and iodine employed is sufficient to provide from about 0.5 to about 40 weight percent of the polymer/iodine complex in said cyanoacrylate ester such that the resulting composition polymer film is antimicrobial.

19. The method according to Claim 18 wherein the cyanoacrylate ester composition further comprises a polymerization inhibitor.

20. The method according to Claim 19 wherein said polymerization inhibitor is a mixture comprising hydroquinone and $SO_2$.

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/30233

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(7) : A01N 25/00,59/12; A61K 47/48
US CL : 424/667,Dig.6; 514/772,772.1,772.3,785,788,836,970
According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/667,Dig.6; 514/772,772.1,772.3,785,788,836,970

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Extra Sheet.

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| Y | US 5,807,563 A (ASKILL et al.) 15 September 1998, col. 4, lines 13-16, col. 5, lines 14-56, col. 6, lines 53-67, col. 9, lines 60-68, col. 10, lines 1-9, 30-48. | 1-20 |
| Y | US 5,335,373 A (DANGMAN et al.) 09 August 1994, col. 23, lines 23, 26, 31-33, col. 24, lines 39-46, col. 26, lines 33-35, 41-44. | 1-20 |

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

| | | | |
|---|---|---|---|
| * | Special categories of cited documents: | "T" | later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention |
| "A" | document defining the general state of the art which is not considered to be of particular relevance | "X" | document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone |
| "E" | earlier document published on or after the international filing date | "Y" | document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art |
| "L" | document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) | "&" | document member of the same patent family |
| "O" | document referring to an oral disclosure, use, exhibition or other means | | |
| "P" | document published prior to the international filing date but later than the priority date claimed | | |

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 23 FEBRUARY 2000 | 06 MAR 2000 |
| Name and mailing address of the ISA/US<br>Commissioner of Patents and Trademarks<br>Box PCT<br>Washington, D.C. 20231 | Authorized officer<br>FRANK CHOI |
| Facsimile No. (703) 305-3230 | Telephone No. (703) 308-1235 |

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# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/30233

B. FIELDS SEARCHED
Electronic data bases consulted (Name of data base and where practicable terms used):

APS Messenger, STN/CAS, WEST
search terms: cyanoacrylate, iodine, polyoxyalkylene, polyalkylene, polyoxyethylene, polyoxypropylene, polyethylene, polypropylene, polymer, copolymer, terpolymer, plasticizer, polymerization inhibitor, hydroquinone, sulfur dioxide